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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,966	11/03/2003	John Henry Kenten	100390-03578	5067

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	**PAPER NUMBER**
1652	

NOTIFICATION DATE	DELIVERY MODE
07/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/699,966	KENTEN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/27/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *174-176* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *174-176* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 124-127 and 133-181 are pending. Claims 123-127, 133-173 and 177-181 remain withdrawn. Claims 174-176 were examined in the prior action. With supplemental amendment of this application, the applicant, on date 02/27/08 amended claim 176.

Claim Rejections

35 U.S.C 112 second paragraph

Rejections of claim 174-175 are withdrawn after amendment of the claims and applicant argument found to be persuasive.

35 U.S.C 112 1st paragraph Written Description requirement.

Claims 174-176 are rejected under 35 U.S.C. 112, first paragraph for lack of Written Description for the reasons set forth in the previous office action mailed 08/29/2007. Claims 174-176 are directed to antibody conjugates comprising VH region of any antibody conjugated to VL region of any other antibody and further conjugation of thereof having any structure and function. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of antibody or catalytic antibody. Claimed class of antibody conjugate comprising VH and VL region comprise any protein molecule having any structure and function. Although VH region of an antibody comprise a less variant structure (most VH region of any antibody have defined structure) but VL region of an antibody has variable structure. Without any

structural knowledge one skilled in art unable to make and use such antibody conjugate comprising VH region of any antibody conjugated to VL region of any other antibody. Furthermore no relationship between the antibody to any antigen in case of antibody and to any hapten molecule in the case of catalytic antibody is given. Production of specific antibody depends on the structure and nature of antigen and catalytic antibody depends on the structure of the specific transition state analog (Mader et al.). In most cases, even a single hapten molecule of a transition state analog (for forming or cleaving a bond) elicits multiple catalytic antibodies (Benzoic et al). Therefore, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Therefore, one of skill in the art would not recognize that applicants' were in possession of the claimed invention.

Applicants' are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants' arguments filed on 02/27/2008 have been fully considered, but they are found unpersuasive. Applicants argue that specification gives ample example of biological constructs of antibodies, production of bispecific antibodies, use of antibodies and prior art teach how to make antibodies and there are ample example of use of bispecific antibodies. However instant claims recite antibody conjugate comprising VH and VL region from different antibodies comprising any protein molecule having unspecified structure, function and conjugated together with a linker having unspecified

structure. As explained in prior action and above, overall structure of an antibody is critically important to its function (binding an antigen) and much of this structure of natural antibodies is NOT provided by the claimed constructs. Any polypeptide conjugate comprising VH region of any antibody conjugated to VL region linked with any linker region with any structure will not suffice to produce successful single chain antibodies since not all linkers will result in the correct structures of the variable regions nor to correct alignment of the structure of VL to bind the hapten. Furthermore the presence of multiple variable regions which bind to the same hapten within natural antibodies is important for providing sufficient binding affinity such that it is not clear one could produce single chain antibodies in which the VH and VL regions are from antibodies with varying specificity. Applicant further argue that production of bispecific proteins, or fusion proteins comprising enzyme fused to antibody using recombinant DNA technology is well known in prior art. Production of enzyme-antibody conjugate comprising fusion of gene encoding an enzyme of known structure and function with a gene encoding an antibody having desired function (binds to known antigen) is known. However; as explained above instant claims comprise single chain polypeptide molecule comprising any VH region of any antibody conjugated to any VL region of any structure linked with any linker region with any structure having no structure-function correlation. While one could produce a single chain polypeptide molecule comprising VH region of an antibody conjugated to a VL region of another antibody linked with a linker by recombinant DNA technology; however, as explained above it will not suffice to produce successful single chain antibodies since not all linkers will result the correct

structures of the variable regions nor to correct alignment of the structure of VL to bind the hapten. Moreover, no relationship between the antibody to any antigen is given. Without knowing the antigen of an antibody, one can not make and use such an antibody. Therefore, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Finally applicants arguments in conjunction with all legal decisions have been fully considered but not been found convincing because the claims do not recite a fully characterized antigen. The court (69 USPQ2d 1508 Noelle V. Lederman, (Fed. Cir. 2004)), in contrast to applicants arguments, recites at pages 1513-1514 that the court adopted the USPTO guidelines " claim directed to any antibody which is capable of binding to antigen "X" would have sufficient support in a written description that disclosed fully characterized antigens.

35 U.S.C 112 1st paragraph Enablement requirement

Claims 174-176 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement for the reasons set forth in the previous office action mailed 08/29/2007.

Claims 174-176 are rejected under 35 U.S.C. 112, first paragraph are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibody VH region of monoclonal antibody B72.3 (specific to cancer) conjugated to VL region of a catalytic antibody (CAB) elicited against a phosphonate hapten for 5-fluorouridine 5-)2,4,6 trimethylbenzine, does not reasonably provide enablement for any antibody conjugate comprising VH region of any antibody molecule conjugated to VL

region of any antibody and further conjugate thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and for use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claim(s).

These claims are so broad to encompass antibody conjugate comprising VH region of any antibody molecule conjugated to VL region of any antibody and further conjugate thereof. The antibody conjugates claimed herein comprising any molecule having any structure and any function. The specification discloses the structure and function of a few antigen and haptens and suggestion of eliciting antibodies and catalytic antibodies against them. The structure of the hapten and function is very crucial in antibody catalysis and production of specific catalytic antibody depends on the structure of the specific transition state analog. Production of antibody depends on the structure and function of the antigen. Finding a suitable transition state analog for any molecule and producing CAB for said reaction, and finding which among enormous number of variants of CAB has desired properties (catalyze said reaction) requires

that one of ordinary skill in the art know or be provided with guidance for the selection of hapten to elicit suitable AB for production of CABs. Similarly to raise an antibody, one of ordinary skill in the art must know or be provided with guidance for the selection antigen to elicit antigenic reaction for the production of said antibodies and in the instant case in order to produce chimeric antibodies as claimed, specific structural information about the VH and VL regions of the parent antibodies is needed as such chimeric antibodies can not be produced by immunization of a animal. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Making an antibody conjugate comprising VH region of any antibody molecule conjugated to VL region of any catalytic antibody and further conjugate thereof without knowing the structure and function of corresponding antigen and hapten is unpredictable.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any conjugate comprising VH region of any antibody molecule conjugated to VL region of any catalytic antibody and further conjugate thereof. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient

guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicants' arguments filed on 02/27/2008 have been fully considered, but they are found unpersuasive. Applicants argue that generation of antibody based on skill in the art, detailed description in the specification is not undue. Applicant further argue that considerable amount of experiment is permissible, if its merely routine. It is true that generation of antibody is not undue provided that an antigen is known for the antibody. However,these claims do not recite a fully characterized antigen. One skill in the art need to perform infinite numbers of experiment to find out what are the haptens for the antibody recited in these claims. Moreover instant claims recite antibody conjugate comprising VH and VL region from different antibodies comprising any protein molecule having unspecified structure and function and conjugated together with a linker having unspecified structure. Overall structure of an antibody is critically important to its function (binding an antigen). Any polypeptide conjugate comprising VH region of any antibody conjugated to VL region linked with any linker region with any structure will not suffice to produce successful single chain antibodies since not all linkers will result in the correct structures of the variable regions. Furthermore the presence of multiple variable regions which bind to the same hapten is important for the overall binding affinity of natural antibodies such that it is not clear one could produce single chain antibodies in which the VH and VL regions are from antibodies with varying specificity

with similar binding affinity. Therefore making an antibody conjugate comprising VH region of any antibody molecule conjugated to VL region of any antibody without knowing their actual structures correlate its binding to any antigen /or hapten is unpredictable. Without knowing the specific antigen one of ordinary skill in the art would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

CLAIM Rejection - 35 U.S.C 102

Rejection of claims 174-176 under 35 U.S.C. 102(b) as being anticipated by Novotny et al. (PNAS 1985, 82, 4592-4596) is withdrawn after amendment of the claims and also finding applicants argument persuasive.

Rejection of claims 174-176 are under 35 U.S.C. 102(b) as being anticipated by Scott et al. (J. Immun. 1989, 143, 293-298) is withdrawn after amendment of the claims and finding applicants argument persuasive.

However a new 35 USC 102 rejection is applied as follows:

Claims 174-176 are rejected under 35 U.S.C. 102(b) as being anticipated by Holliger et al. (PNAS 1993, 90, 6444-6448, from IDS). Holliger et al. teach a single

chain bispecific antibody comprising antibody conjugate comprising V_HA-V_LB and V_HB-V_LA wherein V_H region of one antibody fragment (mouse hybridomas NQ11) is conjugated to V_L region of another antibody fragment (D1.3, anti-hen egg lysozyme (HEL) by a 15 residues linker (page 6444 3rd paragraph, also FIG 1 and Table 1).

Applicants' amendment of the claims necessitates the above new rejection and therefore this office action is made final.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat. T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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